

**EXCELLENT OUTCOMES IN COMBINED LIVER-KIDNEY TRANSPLANTATION:
IMPACT OF KDPI AND DELAYED KIDNEY TRANSPLANTATION**

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KEY WORDS

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ABBREVIATIONS

CIT = cold ischemia time

CLKT = combined liver-kidney transplantation

DCD = donation after circulatory death

DGF = delayed graft function

ECD = extended criteria donor

GFR = glomerular filtration rate

KT = kidney transplantation

LT = liver transplantation

MELD = model for end-stage liver disease

UNOS = United Network for Organ Sharing

ABSTRACT

The positive impact of delayed kidney transplantation (KT) on patient survival for combined liver-KT (CLKT) has already been demonstrated by our group. The purpose of this study is to identify whether the quality of the kidneys (based on KDPI) or the delayed approach KT contributes to improved patient survival. 130 CLKT were performed between 2002-2015; 69 with simultaneous KT (Group S) and 61 with delayed KT (Group D) (performed as a second operation with a mean cold ischemia time [CIT] of 50 ± 15 h). All patients were categorized according to the KDPI score; 1-33%, 34-66%, and 67-99%. Recipient and donor characteristics were comparable within Groups S and D. Transplant outcomes were comparable within Groups S and D, including liver and kidney CIT, warm ischemia time, and delayed graft function. Lower KDPI kidneys (<34%) were associated with increased patient survival in both groups. Combination of delayed KT and KDPI 1-33% resulted in 100% patient survival at 3-years. These results support that delayed KT in CLKT improves patient survival. The combination of delayed KT and low KDPI offers excellent patient survival up to 3-years. Improved outcomes in the delayed KT group including high KDPI kidneys supports expansion of the donor pool with the use of more ECD and DCD kidneys.

INTRODUCTION

As many as 30% of liver transplant (LT) recipients have renal insufficiency at the time of transplantation (1-3). As a direct consequence of the introduction of the MELD (model for end-stage liver disease) score in 2002, which includes serum creatinine as one of its parameters, there was a predictable increase in the total number of combined liver-kidney transplants (CLKT) performed annually, as patients with renal failure had a consistently higher MELD score (4,5). In 2015, more than 600 CLKT were performed in the U.S, which was approximately 10% of all LT activity (4-6). Despite the continuous increase in CLKT in the last decade, until very recently there was no 'standardized' policy by the UNOS (United Network of Organ Sharing) for CLKT until 2016 (7,8). In 2016, the new Simultaneous Liver-Kidney Allocation policy was introduced with a proposal to include medical eligibility criteria and a safety net for any liver recipient requiring a subsequent kidney transplant (KT) within the first post-transplant year (5,6). Before the introduction of this allocation policy, Nadim et al. conducted a survey of 88 transplant centers that perform CLKT in the U.S. and found that the majority of centers (73%) used dialysis duration (varying between >4 to >8 weeks) for acute renal failure as a cut-off for CLKT listing. There were also 30% of centers that used 'any' acute kidney injury alone as adequate criterion for determining the need for CLKT (9). Following the introduction of the new Simultaneous Liver-Kidney Allocation policy, the current situation is not different, as most recently shown by Luo et al (10). They have shown that among eligible patients, only 26% were listed for CLKT and the variation of the listing probability based on the new 'medical eligibility criteria' ranged from 2.5% to

100% overall, and 1% to 53% in high volume transplant centers (>100 total CLKT-eligible patients) (10).

In 2016, 2 different groups showed the impact of the quality of kidney allografts on patient survival in CLKT based on kidney donor risk index (KDRI) or kidney donor profile index (KDPI) scores using the Scientific Registry Transplant Recipients (SRTR) database (6,11). Sharma et al. showed that there was no survival benefit of CLKT over LT alone, unless the KDRI was ≤ 1.1 (KDPI equivalence ~60-65%) (11). They also showed that 76% of CLKT recipients received kidneys with a KDPI $< 65\%$ (KDRI ≤ 1.1) (11). Formica et al. showed that 48% of recipients of CLKT had kidneys with a KDPI of $< 35\%$ and 37% of CLKT recipients received no dialysis prior to transplantation (6).

Although Formica et al. (6) showed the importance of the duration of pre-transplant dialysis and of chronic kidney disease with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m² before transplant on patient survival in CLKT, Sharma et al. (11) did not include this important variable in their study. In 2017, another SRTR database analysis by Jay et al. (12) confirmed the impact of KDPI on patient survival undergoing CLKT. They showed that there is a significantly increased mortality in recipients of CLKT when they receive kidney grafts from higher KDPI, especially with KDPI $> 85\%$ (HR=1.83, 95%CI=1.44-2.31) (12).

Most recently, we reported improved patient and graft survival using a novel approach in CLKT (13). The rationale of this novel approach (delayed implantation of the kidney graft up to 2-3 days in CLKT) was to offer a less hostile environment with a more stable

recipient at the time of KT. The thought behind our delayed approach was due to the opposite requirements of the kidney and liver grafts in the immediate post-operative management and also the effect of kidney injury and loss of GFR immediately following LT, especially within the first 48h (3,14). The most interesting finding in our recent study was that delayed graft function (DGF) of the kidney graft (HR= 166, 95%CI=9-2926) and the use of ECD kidneys (HR=16, 95%CI=2-145) which were significant negative independent risk factors for patient survival (13).

In the current study, we aimed to identify whether the quality of the kidneys (based on KDPI) or the delayed approach KT prolonged patient survival in a homogenous cohort of CLKT recipients.

MATERIALS AND METHODS

All medical records of an observational cohort (n=130) of CLKT performed at Indiana University Hospital between 03/2002 to 10/2015, were reviewed. Inclusion criteria for the data analysis included all adult (≥ 18 years old) transplant recipients undergoing CLKT, including kidney or liver re-transplants. There were no exclusions for intraoperative or perioperative mortality or graft loss, for non-transplant-related deaths, or for noncompliance. Retrospective review and analysis of data from the transplant center database was approved by the Institutional Review Board of Indiana University School of Medicine.

Indications and definitions

Two eras were defined for the current study, where the KT was performed either 'simultaneously' with LT at the same operation (first era 03/2002-06/2007), or 'delayed' (delayed up to 81 hours and performed at a later time as a second operation) (second era 06/2007-10/2015). Therefore, data analysis was performed in both eras separately in order to make analysis as homogenous as possible for surgical techniques and clinical experience in patient management. Recipient listing for LT was according to standard criteria and protocols as established by our center and UNOS. Patients who required CLKT were listed according to their $\text{eGFR} < 30 \text{ mL/min/1.73m}^2$ calculated by the modification of diet in renal disease formula prior to transplant for chronic renal failure, or their need for dialysis for > 8 weeks, as proposed by UNOS (1,2,8,9). DGF was defined as the need for dialysis within the first 7 days following KT. Kidney graft

failure was defined as removal of the graft or complete loss of graft function requiring retransplantation or permanent dialysis. Graft function was monitored clinically and by laboratory values (serum creatinine and eGFR).

In the first era, KT was performed following the implantation of the liver but during the same operation (simultaneously) (Group S, n= 69). In the second era, KT was 'delayed' up to 81 hours and performed as a separate operation (Group D, n= 61). Despite two separate transplants in Group D, the procedure was listed as CLKT in the SRTR registry. Three different subgroups were further defined for each era according to the KDPI quartile, such as KDPI 1-33%, KDPI 34-66%, and KDPI 67-99%. KDPI quartiles were divided into 3 equal parts due to the limited sample size in each group and this allowed us to evenly stratify the risk factors for each increase in KDPI quartile.

Surgical techniques

Standard surgical techniques were applied for the procurement of deceased donor livers and kidneys, and cold preservation, as previously described (3,13). At our center, all deceased donor kidney allografts are routinely maintained on continuous hypothermic pulsatile machine perfusion (Waters IGL perfusion machine) (Waters Medical Systems, Rochester, MN). All kidneys transplanted in both eras were maintained by machine perfusion either for 3-5 hours in Group S or up to 81 hours in Group D, as previously described (13,15). More than 95% of LT cases were performed using a piggyback technique. Details of this approach and other details about the LT operation performed at our center have been reported previously (16). In both Groups S

and D, all recipients were supported by continuous veno-venous hemodialysis initiated at the time of LT, and continued until the KT was complete. In Group D, continuous veno-venous hemodialysis was continued in the intensive care unit between LT and KT.

Immunosuppressive therapy and infection prophylaxis

Details of the immunosuppressive regimen and prophylaxis against cytomegalovirus and *Pneumocystis jiroveci* pneumonia in LT recipients have been reported previously (16). Briefly, induction therapy included rabbit antithymocyte globulin (rATG) (2 mg/kg for 3 doses), and anti-CD20 monoclonal antibody (Rituximab, single dose 1.5 mg/m², maximum 300 mg). The only difference between in the immunosuppressive regimen between Group S and Group D was the administration of the first dose of rATG on post-operative day 1 and day 2, respectively. In Group D, rATG was administered before the implantation of the kidney allograft. A methylprednisolone bolus was administered as premedication for each of the three rATG infusions, and then was discontinued completely. Maintenance immunosuppressive therapy included tacrolimus (target trough levels of 7-10 ng/dL for the first 3 months post-transplant, and 6-8 ng/mL, thereafter), and mycophenolate mofetil (1000 mg twice daily).

Statistical analysis and end-points

The primary end-point was patient survival after CLKT in both eras. Secondary end-points included DGF, early and late kidney allograft losses, and kidney allograft function.

The data were summarized using means with standard deviations, or medians with interquartile ranges for continuous variables, and percentages for discrete variables.

Continuous variables were analyzed using Wilcoxon-Mann-Whitney test. For discrete variables, the Chi-square analysis was performed unless the event number for the given group was ≤ 5 , in which case Fisher's Exact test was performed. Patient survival probability was estimated using the Kaplan-Meier method, and differences in the curves were analyzed using a log-rank test. All statistical calculations were performed by SAS v9.4 (SAS Institute Inc, Cary, NC, USA). Images were created using GraphPad Prism 6 for MAC OS X (La Jolla, CA, USA). A p value of <0.05 was considered statistically significant.

RESULTS

Donor and recipient demographics were comparable within Group S ([Table 1](#)) and Group D ([Table 2](#)) among their subgroups, including recipient age, percentage of older recipients >60 years, recipient body mass index, primary indication for transplant, Hepatitis C status, panel reactive antibody status, cytomegalovirus risk, MELD score, retransplantation status, rate and duration of dialysis before CLKT, and duration of eGFR<30 mL/min for pre-emptive patients for the portion of KT of CLKT. As expected, variables which contributed to the calculation of KDPI were higher in higher KDPI subgroups, such as D-MELD, donor age, cause of death, extended criteria donor (ECD) kidneys, and donor KDPI ([Tables 1 and 2](#)). ECD kidneys were used in 6% of transplants in the first era in Group S, and their use reached to 50% in the highest KDPI subgroup. The use of ECD kidneys was higher in the second era in Group D compared to Group S (15% of all activity vs. 6%, $p<0.01$). In Group D, ECD kidneys constituted 64% of all kidney grafts in the highest KDPI subgroup, and 14% of all kidney grafts in the middle KDPI subgroup (KDPI 34-67%). The same trend was seen in the use of DCD (donation after circulatory death) donors between Group S and Group D with a rate of 1% and 11% ($p<0.01$), respectively ([Tables 1 and 2](#)).

Transplant clinical outcomes are shown in [Table 3](#) for Group S and in [Table 4](#) for Group D. The mean kidney CIT was 9.9 ± 2.9 hours in the first era when KT was performed simultaneously (Group S). In the second era, when delayed approach of KT was preferred in CLKT (Group D), the mean kidney CIT was 50.2 ± 14.9 hours ($p<0.001$).

Mean kidney and liver CIT and warm ischemia time in subgroups among Groups S and D were similar ([Tables 3 and 4](#)). DGF was seen in the first era in Group S (7.3%), with higher rates in higher KDPI groups. However, no DGF was observed in the second era, in Group D regardless of KDPI, despite >50 hours of kidney CIT.

Transfusion requirements (packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate), intensive care unit stay, and hospital stay were similar in all subgroups both in Groups S and D, except highest KDPI subgroup (67-99%) in Group D which had longer ICU stays. In the first era, recipients were kept longer in the ICU (14 days), however in the second era the ICU stays was shorter (~8-9 days) ([Tables 3 and 4](#)). In the first era (Group S), kidney loss within 90 days and 1 year post-transplantation was higher in higher KDPI subgroups (KDPI >34%) ([Table 3](#)). This trend was similar also in death rates within 90 days and 1 year post-transplantation since DGF strongly contributed to patient death. However, in the second era (Group D), kidney loss occurred most frequently due to patient death (with functioning kidney) related to cardiogenic or other reasons. In fact, kidney loss mirrored the rate of patient death 1 year post-transplantation in Group D ([Table 4](#)).

Serum creatinine levels among surviving patients at 1-month, 6-month, 1-year, 2-year, and 3-year post-CLKT were similar in both eras. The impact of KDPI was obvious on patient survival regardless of whether CLKT was performed simultaneously in the first era, or with the delayed approach in the second era ([Figure 1](#)). In the first era (Group S), the lowest KDPI group (1-33%) had 90% patient survival at 3-year post CLKT. The

survival percentage decreased to 65% with the increase of KDPI to 34-66%, and to 55% with a KDPI of 67-99% at 3-year post-transplant (log-rank test, $p=0.0191$). The same trend was also observed in the second era (Group D). Excellent patient survival (100% at 3-year) was achieved with the best kidneys (KDPI 1-33%). Although patient survival decreased when higher score KDPI kidney grafts were used (log-rank test, $p=0.01$), it was still better compared to the first era (Group S), despite the fact that significantly more ECD and DCD kidneys were utilized in the second era (Group D).

In order to understand the residual native kidney function on patient and graft survival and also kidney function post-CLKT, we analyzed the data from recipients who were on dialysis >3 months before CLKT. There were 39 patients (56%) and 33 patients (54%) received >3 months of dialysis before CLKT in Group S and Group D, respectively ($p=0.92$). The outcomes among those recipients who had >3 months of pre-transplant dialysis were similar between Groups S and D.

Of note, in Group D, one DCD kidney recipient, who was very frail, lost his kidney graft on post-operative day 8 due to venous thrombosis and underwent transplant nephrectomy. The patient died 6 months after the nephrectomy due to cardiovascular causes. This patient belonged to the middle KDPI subgroup (34-67%). Other causes of death in Group D were sepsis ($n=2$), malignancy ($n=1$), multiorgan failure ($n=1$), and unknown ($n=2$). In Group S, sepsis ($n=6$) was the leading cause of death, followed by malignancy ($n=5$), liver failure ($n=4$), multiorgan failure ($n=3$), cardiovascular causes ($n=2$), renal failure ($n=2$), and unknown causes ($n=9$).

DISCUSSION

The KDPI score for the allocation of KT has been introduced as an aid to evaluate deceased donor kidney offers. Since its introduction, more data and outcomes have been obtained with the use of low and high KDPI kidney grafts and it was shown that recipients of high KDPI kidneys experience higher rates of DGF and renal dysfunction, and worse clinical outcomes compared to recipients with low KDPI kidneys (17,18). It is well known that peri-operative kidney dysfunction is a well-established risk factor for recipient mortality in patients undergoing LT (19-21), and also CLKT (13,22,23).

Historically, the CLKT procedure was performed as a single contiguous procedure in which the KT immediately follows the LT. The severity of underlying disease, and the complexity of the surgical procedure, render the kidney allograft more susceptible to DGF when it is simultaneously transplanted at the time of LT (24). Moreover, liver and kidney allografts have opposite needs in the immediate post-operative period up to 2-3 days. For example, liver allograft function is optimized with a low central venous pressure and an even fluid balance, which minimizes graft congestion. However, the kidney allograft performs poorly in the face of low central venous and systolic pressures, or when vasopressors are required to maintain blood pressure, which is often common in the immediate post-LT period. Additionally, the kidney allograft is compromised by significant hepatic reperfusion injury and elevated bilirubin levels, both of which damage renal tubules, creating acute tubular necrosis. This phenomenon results in a decrease of 15-20% of eGFR in the first 2-3 days post-LT (3).

With this in mind, we introduced a novel approach of delaying the KT until the recipient of LT have an opportunity to resolve coagulopathy, reduce or stop pressor support, decompress varices, and to clear post liver reperfusion debris that could compromise kidney function. Our novel approach (delaying the KT 2-3 days in CLKT) improved patient graft survival with no DGF (13). Although a single center study (22) and the SRTR database analysis (12) claim that longer kidney CIT predicts worse outcomes in CLKT, in our experience, using pulsatile hypothermic perfusion preservation, we did not observe any DGF despite an average of 50 hours (up to 81 hours) of CIT in Group D.

A recent analysis by Lunsford et al. further confirms the importance of delaying the KT in CLKT and the rationale behind our Indiana approach (22). In their study, they sought to evaluate renal allograft futility (patient death or need for renal replacement therapy at 3 months) in 331 patients who were listed for simultaneous liver-kidney transplantation. Of 331 patients, 171 (52%) died in the waiting list, 145 patients (44%) underwent CLKT, and 15 (5%) underwent LT alone. Of 145 who received CLKT, 39% experienced DGF, and 21% either died or needed a renal replacement therapy within 3 months after transplantation. They concluded that KT should be deferred in liver recipients at high risk for renal allograft futility (22). Another recent study reported long-term renal allograft survival and patient survival when KT was performed sequentially (delayed) after LT in CLKT from the same living donor (25). Most recently in 2017, Lunsford et al. (31) have confirmed that delayed renal implantation with the use of hypothermic machine perfusion improve survival following CLKT. Wadei et al. (24) reported an overall DGF rate of 26% in simultaneous CLKT, which was higher when DCD donors were used

(42%). According to the SRTR database, the rate of DCD kidneys used in CLKT was only 3% (12). However, in the current study, we used higher rates of DCD kidneys (11%) and ECD kidneys with similar or better outcomes in the second era (Group D), and we observed very low or no DGF both in the first and second eras. We believe that the lower or no DGF was due to (i) the use of hypothermic pulsatile machine perfusion (26), which was utilized for all kidney grafts, even for the short time between organ procurement and kidney implantation in simultaneous CKLT (Group S), or for several hours (up to 81h) (Group D) which helped the clearance of the products of anaerobic metabolism and minimizing vasospasm (26,27), and (ii) the delayed approach KT (13), as explained above. Korayem et al (32) have recently shown that hypothermic pulsatile machine perfusion of kidney allografts plays a key role in preventing DGF among patient listed for CLKT, confirming our findings.

As the importance of peri-operative renal dysfunction and DGF become more evident in LT, and especially in CLKT, the discussion on the impact of KDPI on patient survival undergoing CLKT has blossomed due to the well-known higher DGF rates in patients with higher KDPI kidneys (6,12,17,29). Several groups studied the SRTR database with different variables in order to understand the impact of the quality of kidney grafts in CLKT (6,11,12,29). Despite the statistical power obtained by the increased number of patients, the limitation of these studies is the inhomogeneity of the SRTR database, which makes the interpretation of outcomes difficult. In the current study, we observed more deaths in Group S when KDPI was >34%. In those subgroups (KDPI 34-66% and 67-99%), DGF rates were 15% and 13%, respectively (Table 3). Moreover, due to the

nature of KDPI calculations those groups by definition included ECD kidneys. These two factors, DGF and ECD, have been previously shown to be the most significant independent negative predictors of patient survival (13). Therefore, delayed approach KT might prove be even more beneficial for kidneys with a KDPI of >34% than those of <34%.

The current study not only confirmed the importance of the delayed approach to KT in CLKT, but also analyzed the impact of KDPI in two different homogenous cohorts in two eras. The current study also confirmed the findings by Sharma et al. (11) on the positive impact of low KDPI on patient survival following CLKT. However, it also showed that the combination of delayed KT and the use of kidney grafts with a KDPI of 1-33% enables 100% patient survival at 3-year after transplantation. However, we also believe that we were more adept in the second era with liver transplant surgeries, patient management, and intensive care unit which also contributed to the achievement of these outcomes.

The most interesting finding was discussed by Formica et al. (6) regarding better allocation of CLKT in order to come up with a new plan to utilize better quality kidneys for pediatric recipients, since currently 48% of CLKT recipients received kidneys with a KDPI of <35%. In our study, while 59% of kidneys had a KDPI of 1-33% in the first era, the rate dropped to the similar rates as the SRTR database (49%) in the second era with the use of more ECD kidneys. Although Levitsky et al. (30) showed that the use of ECD kidneys in simultaneous liver-kidney transplantation corresponds with a 30% decrease in patient survival compared to non-ECD kidneys, we did not observe this

decrease in our analysis. Further discussion has taken place by other groups regarding the high mortality of recipients with the use of high KDPI kidney grafts in CLKT (12). More evidence from the SRTR or larger databases considering important variables, such as the era effect, recipient pre-transplant dialysis and/or pre-emptive status and their duration, and immunosuppressive regimens will be needed to draw solid conclusions.

The present study has limitations, particularly the single center retrospective non-randomized study design. However, the study population represents a very homogeneous cohort of recipients which controls for the 'era effect', primary surgical team, surgical techniques, immunosuppressive regimens, and patient management, which are all important variables affecting clinical outcomes. Another limitation was the relatively small number of recipients in the highest KDPI (67-99) subgroups in both eras (8/69, 12% in Group S and 9/61, 15% in Group D). The SRTR database had only 257 patients with a KDPI >85% over 12 years (12), which makes 6% (257/4207) of the total CLKTs.

In conclusion, with further evidence of the recent (13) and current study and by other high-volume transplant centers (22), we believe that delayed KT in CLKT should be the preferred approach whenever possible. The impact of delayed KT on patient survival seemed more prominent in higher KDPI groups (KDPI>34%). The delayed approach to KT certainly facilitates expansion of the donor pool by allowing the use of more ECD and DCD kidneys with similar or even better outcomes. Further discussion is needed to

consider the patient survival goal in CLKT in order to allocate lower KDPI kidneys (<35%) to the pediatric recipients.

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AUTHORS CONTRIBUTIONS

Drs. Ekser and Mangus had full access to all of the data in the study.

Study concept and design: Ekser, Goggins, Fridell,

Acquisition, analysis, or interpretation of data: All authors.

Drafting the manuscript: Ekser.

Critical revision of the manuscript for important intellectual content: All authors.

DISCLOSURE

All authors declare no conflict of Interest including manuscript preparation or funding by a commercial organization.

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Table 1: Donor and recipient demographics in Simultaneous Kidney Transplantation in Combined Liver-Kidney Transplantation

	Total (n=69)	Group S1 KDPI 1-33% (n=41)	Group S2 KDPI 34-66 (n=20)	Group S3 KDPI 67-99% (n=8)	p
Recipient Demographics					
Age (years) (mean±SD)	54.7±10.6	53.2±12.1	55.8±7.7	59.6±7.1	0.26
Age >60 years (n, %)	23, 33.3%	12, 29.3%	7, 35%	4, 50%	0.53
Gender (n, %)					0.74
<i>Male</i>	50, 72.5%	31, 75.6%	14, 70%	5, 62.5%	
<i>Female</i>	19, 27.5%	10, 24.4%	6, 30%	3, 37.5%	
Race (n, %)					0.02
<i>White</i>	56, 81.2%	37, 90.2%	15, 75%	4, 50%	
<i>African American</i>	10, 14.5%	2, 4.9%	4, 20%	4, 50%	
<i>Other</i>	3, 4.4%	2, 4.9%	1, 5%	0, 0%	
Blood Type (n, %)					0.29
<i>A</i>	33, 47.8%	23, 56.1%	7, 35%	3, 37.5%	
<i>B</i>	4, 5.8%	2, 4.9%	2, 10%	0, 0%	
<i>AB</i>	4, 5.8%	1, 2.44%	3, 15%	0, 0%	
<i>O</i>	28, 40.6%	15, 36.6%	8, 40%	5, 62.5%	
Body Mass Index (kg/m ²) (mean±SD)	27.9±4.7	28.0±5.2	27.2±4.1	29.7±3.4	0.46
Primary Indication for Transplant (n, %)					0.79
<i>ETOH</i>	11, 15.9%	6, 14.6%	4, 20%	1, 12.5%	
<i>Hepatitis C</i>	21, 30.4%	13, 31.7%	6, 30%	2, 25%	
<i>Autoimmune Liver Disease</i>	11, 15.9%	6, 14.6%	5, 25%	0, 0%	
<i>NASH</i>	12, 17.4%	8, 19.5%	2, 10%	2, 25%	
<i>Other</i>	14, 20.3%	8, 19.5%	3, 15%	3, 37.5%	
Hepatitis C Positivity (%)	40.6%	43.9%	30%	50%	0.56
PRA (%)					
Class I	14.5%	19.5%	5.0%	12.5%	0.36
Class II	15.9%	19.5%	10.0%	12.5%	0.79
Cytomegalovirus Status (%)					0.61
D-/R-	10%	7%	20%	0%	
D-/R+	25%	29%	20%	13%	
D+/R-	14%	12%	15%	25%	
D+/R+	51%	51%	45%	63%	
MELD (mean±SD)	26.5±8.9	28.1±9.0	25.4±9.3	26.3±6.0	0.11
D-MELD (mean±SD)	921±412	725±283	1184±432	1265±360	<0.001
Previous Kidney Transplant (%)	4%	7%	0%	0%	0.69
Previous Liver Transplant (%)	16%	15%	15%	25%	0.71
Dialysis Before Transplant (%)	68%	71%	65%	63%	0.81
Duration of Dialysis Before Transplant (days) (median, IQR)	360, 180- 360	360, 180- 720	270, 90- 360	180, 118-270	0.60
Duration of eGFR <30mL/min/1.73m ² For Patients Who Were Not On Dialysis (days) (median, IQR)	90, 56-165	90, 56-180	90, 56-180	90, 56-120	0.74

Donor Demographics					
Age (years) (mean±SD)	36.6±14.7	26.9±9.2	47.4±6.5	59.5±4.7	<0.001
Gender (%)					0.09
<i>Male</i>	55%	66%	40%	37.5%	
<i>Female</i>	45%	34%	60%	62.5%	
Body Mass Index (kg/m ²) (mean±SD)	26.1±6.4	26.4±7.5	26.7±3.7	22.5±5.0	0.25
Cause of Death (%)					<0.001
<i>Stroke (0)</i>	39%	17%	70%	75%	
<i>Trauma (1)</i>	43%	66%	15%	0%	
<i>Anoxia/Other (2)</i>	17%	17%	15%	25%	
Donor Hepatitis C Positivity (%)	3%	0%	5%	13%	0.08
Extended Criteria Donor Kidneys (%)	6%	0%	0%	50%	<0.001
Donation After Circulatory Death Kidneys (%)	1%	2%	0%	0%	1.0
Donor KDPI (mean±SD) (median, IQR)	(30.8±24.0) (25, 12-48)	(13.7±8.6) (13, 7-18)	(47.4±9.2) (48, 38-53.5)	(76.6±6.8) (76.5, 71-78.5)	<0.001
Donor KDRI (mean±SD) (median, IQR)	(0.8±0.2) (0.8, 0.7-1.0)	(0.7±0.1) (0.7, 0.65-0.74)	(1.0±0.1) (0.98, 0.88-1.035)	(1.3±0.1) (1.3, 1.23-1.325)	<0.001

Legend: D= donor, eGFR= estimated glomerular filtration rate, ETOH= alcoholic liver disease, IQR= interquartile range, KDPI= kidney donor profile index, KDRI= kidney donor risk index, MELD= model for end-stage liver disease, NASH= nonalcoholic steatohepatitis, PRA= panel reactive antibody, R= recipient, SD= standard deviation.

Table 2: Donor and recipient demographics in Delayed Kidney Transplantation in Combined Liver-Kidney Transplantation

	Total (n=61)	Group D1 KDPI 1-33% (n=30)	Group D2 KDPI 34-66 (n=22)	Group D3 KDPI 67-99% (n=9)	p
Recipient Demographics					
Age (years) (mean±SD)	58.3±11.2	57.5±10.3	60.1±10.6	56.4±15.5	0.61
Age >60 years (n, %)	31, 50.82%	14, 46.7%	13, 59.1%	4, 44.4%	0.69
Gender (n, %)					0.87
<i>Male</i>	40, 65.6%	20, 66.7%	15, 68.2%	5, 55.6%	
<i>Female</i>	21, 34.4%	10, 33.3%	7, 31.8%	4, 44.4%	
Race (n, %)					1
<i>White</i>	54, 88.5%	26, 86.7%	19, 86.4%	9, 100%	
<i>African American</i>	4, 6.6%	2, 6.7%	2, 9.1%	0, 0%	
<i>Other</i>	3, 4.9%	2, 6.7%	1, 4.6%	0, 0%	
Blood Type (n, %)					0.39
<i>A</i>	24, 39.3%	13, 43.3%	8, 36.4%	3, 33.3%	
<i>B</i>	10, 16.4%	5, 16.7%	5, 22.7%	0, 0%	
<i>AB</i>	1, 1.6%	0, 0%	0, 0%	1, 11.1%	
<i>O</i>	26, 42.6%	12, 40%	9, 40.9%	5, 55.6%	
Body Mass Index (kg/m ²) (mean±SD)	27.1±5.1	27.2±4.8	26.5±5.5	28.0±5.5	0.76
Primary Indication for Transplant (n, %)					0.97
<i>ETOH</i>	14, 23.0%	6, 20%	6, 27.3%	2, 22.2%	
<i>Hepatitis C</i>	20, 32.8%	8, 26.7%	8, 36.4%	4, 44.4%	
<i>Autoimmune Liver Disease</i>	6, 9.8%	4, 13.3%	2, 9.1%	0, 0%	
<i>NASH</i>	7, 11.5%	4, 13.3%	2, 9.1%	1, 11.1%	
<i>Other</i>	14, 23.0%	8, 26.7%	4, 18.2%	2, 22.2%	
Hepatitis C Positivity (%)	44%	37%	45%	67%	0.28
PRA (%)					
Class I	15%	17%	9%	22%	0.62
Class II	10%	10%	5%	22%	0.35
Cytomegalovirus Status (%)					0.18
D-/R-	7%	7%	5%	11%	
D-/R+	30%	43%	23%	0%	
D+/R-	26%	20%	32%	33%	
D+/R+	38%	30%	41%	56%	
MELD (mean±SD)	27.1±6.9	26.6±6.8	27.2±7.2	28.4±6.9	0.79
D-MELD (mean±SD)	956±478	710±299	1072±502	1510±346	<0.001
Previous Kidney Transplant (%)	3%	3%	5%	0%	1
Previous Liver Transplant (%)	8%	7%	14%	0%	0.56
Dialysis Before Transplant (%)	56%	53%	59%	56%	0.94
Duration of Dialysis Before Transplant (days) (median, IQR)	270, (120- 360)	270, (150- 720)	360, (120- 360)	120, (120- 360)	0.76
Duration of eGFR <30mL/min/1.73m ² For Patients Who Were Not On Dialysis (days) (median, IQR)	120, (90- 180)	120, (56- 120)	120, (90- 180)	150, (105- 180)	0.29

Donor Demographics					
Age (years) (mean±SD)	34.9±13.5	26.3±6.9	39±12.7	53.7±6.7	<0.001
Gender (%)					0.02
<i>Male</i>	64%	80%	55%	33%	
<i>Female</i>	36%	20%	46%	67%	
Body Mass Index (kg/m ²) (mean±SD)	26.8±5.6	26.3±4.4	26.2±6.1	29.7±7.3	0.24
Cause of Death (%)					<0.001
<i>Stroke</i>	21%	3%	23%	78%	
<i>Trauma</i>	44%	67%	32%	0%	
<i>Anoxia/Other</i>	34%	30%	45%	22%	
Donor Hepatitis C Positivity (%)	8%	3%	14%	11%	0.34
Extended Criteria Donor Kidneys (%)	15%	0%	14%	67%	<0.001
Donation After Circulatory Death Kidneys (%)	11%	7%	23%	0%	0.16
Donor KDPI (mean±SD) (median, IQR)	(37.0±24.6) (18.5, 7-28)	(17.6±10.6) (18.5, 7-28)	(45.3±10.3) (42.5, 37-56)	(81.3±7.4) (79, 77-89)	<0.001
Donor KDRI (mean±SD) (median, IQR)	(0.9±0.3) (0.9, 0.8-0.9)	(0.7±0.1) (0.8, 0.7-0.8)	(1.0±0.10) (0.9, 0.9-1.1)	(1.4±0.1) (1.3, 1.3-1.6)	<0.001

Legend: D= donor, eGFR= estimated glomerular filtration rate, ETOH= alcoholic liver disease, IQR= interquartile range, KDPI= kidney donor profile index, KDRI= kidney donor risk index, MELD= model for end-stage liver disease, NASH= nonalcoholic steatohepatitis, PRA= panel reactive antibody, R= recipient, SD= standard deviation.

Table 3: Outcomes in Simultaneous Kidney Transplantation in Combined Liver-Kidney Transplantation.

	Total (n=69)	Group S1 KDPI 1-33% (n=41)	Group S2 KDPI 34-66 (n=20)	Group S3 KDPI 67-99% (n=8)	p
Transplant Outcomes					
Cold Ischemia Time (h) (mean±SD)					
<i>Kidney</i>	9.9±2.9	10.1±2.8	9.9±2.7	8.8±2.8	0.48
<i>Liver</i>	6.7±2.2	6.7±2.2	7.0±2.5	5.8±1.9	0.44
Warm Ischemia Time (min) (mean±SD)					
<i>Kidney</i>	32.7±6.9	32.0±6.5	32.6±5.9	36.1±6.6	0.25
<i>Liver</i>	22.2±4.9	22.0±5.0	22.5±5.1	22.5±4.3	0.91
Delayed Graft Function of Renal Grafts (%)	7.3%	2.4%	15%	13%	0.11
UOP <40 mL within 24h Post-Kidney Transplant (%)	1.5%	0.0%	5%	0%	0.41
Transfusion Requirements During Liver Transplantation (Unit) (%)					
<i>Packed RBCs</i>	100%	100%	100%	100%	1
<i>Fresh Frozen Plasma</i>	87%	97%	100%	86%	0.29
<i>Platelets</i>	54%	57%	63%	14%	0.09
<i>Cryoprecipitate</i>	10%	14%	11%	0%	0.86
Intensive Care Unit Stay (days) (mean±SD) (median, IQR), ¶	(6, 4-17), (13.8±17.9)	(13.8±19.7) (6, 4-17)	(13.2±14.8) (5, 3-22)	(16.0±17.4) (7.5, 5-23.5)	0.93
Hospital Stay (days)(mean±SD) (median, IQR), ¶	(14, 10-28), (23.7±23.3)	(23.9±25.3) (13, 10-26)	(22.8±19.9) (16, 9.5- 29.5)	(25.1±23.5) (15.5, 9-36.5)	0.97
Kidney Loss within 7 days post- transplantation (%)	3%	2%	5%	0%	1
Kidney Loss within 90 days post- transplantation (%)	9%	2%	20%	13%	0.049
Kidney Loss within 1 year post- transplantation (%)	17%	7%	35%	25%	0.02
Death within 7 days post- transplantation (%)	3%	2%	5%	0%	1
Death within 90 days post- transplantation (%)	9%	2%	20%	13%	0.049
Death within 1 year post- transplantation (%)	17%	7%	35%	25%	0.02
Serum Creatinine (mg/dL) (mean±SD)					
<i>1 month</i>	1.33±0.77	1.2±0.5	1.6±1.1	1.6±0.8	0.11
<i>6 month</i>	1.33±0.44	1.3±0.4	1.5±0.6	1.4±0.3	0.12
<i>1 year</i>	1.33±0.44	1.2±0.4	1.5±0.6	1.4±0.4	0.09
<i>2 year</i>	1.49±0.73	1.4±0.7	1.6±0.8	1.5±0.4	0.68
<i>3 year</i>	1.40±0.51	1.3±0.4	1.6±0.7	1.3±0.4	0.24

Legend: IQR= interquartile range, SD= standard deviation, RBC= red blood cells, UOP= urine output. (¶) Median value was used for statistical calculation.

Table 4: Outcomes in Delayed Kidney Transplantation in Combined Liver-Kidney Transplantation.

	Total (n=61)	Group D1 KDPI 1-33% (n=30)	Group D2 KDPI 34-66 (n=22)	Group D3 KDPI 67-99% (n=9)	p
Transplant Outcomes					
Cold Ischemia Time (h) (mean±SD)					
<i>Kidney</i>	50.2±14.9	50.5±14.4	52.6±14.9	42.9±16.6	0.26
<i>Liver</i>	6.0±1.2	5.7±1.1	6.3±1.5	6.2±0.9	0.23
Warm Ischemia Time (min) (mean±SD)					
<i>Kidney</i>	37.9±8.5	39.1±9.4	35.3±7.6	39.9±6.6	0.21
<i>Liver</i>	18.2±4.1	18.0±3.9	18.3±4.6	18.6±3.8	0.92
Delayed Graft Function of Renal Grafts (%)	0%	0.0%	0%	0%	1
UOP <40 mL within 24h Post-Kidney Transplant (%)	0%	0.0%	0%	0%	1
Transfusion Requirements During Liver Transplantation (Unit) (%)					
<i>Packed RBCs</i>	93%	93%	91%	100%	1
<i>Fresh Frozen Plasma</i>	62%	50%	73%	78%	0.17
<i>Platelets</i>	56%	50%	64%	56%	0.60
<i>Cryoprecipitate</i>	11%	10%	18%	0%	0.49
Intensive Care Unit Stay (days) (mean±SD) (median, IQR)¶	(5, 3-12), (12.0±20.2)	(8.8±13.9) (3.5, 2-10)	(8.1±7.3) (5, 3-9)	(31.9±41.0) (14, 7-35)	0.01
Hospital Stay (days) (mean±SD) (median, IQR) ¶	(19, 11-32), (33.3±54.3)	(31.9±71.1) (14, 10-23)	(23.2±10.6) (21.5, 15- 29)	(62.8±47.1) (48, 26-73)	0.18
Kidney Loss within 7 days post- transplantation (%)	0%	0%	0%	0%	1
Kidney Loss within 90 days post- transplantation (%)	7%	0%	18%	0%	0.02
Kidney Loss within 1 year post- transplantation (%)	11%	0%	18%	11%	0.04
Death within 7 days post- transplantation (%)	0%	0%	0%	0%	1
Death within 90 days post- transplantation (%)	5%	0%	14%	0%	0.09
Death within 1 year post- transplantation (%)	8%	0%	19%	11%	0.04
Serum Creatinine (mg/dL) (mean±SD)					
<i>1 month</i>	1.09±0.40	1.1±0.3	1.1±0.5	1.1±0.4	0.79
<i>6 month</i>	1.12±0.31	1.1±0.3	1.1±0.3	1.3±0.5	0.29
<i>1 year</i>	1.15±0.32	1.1±0.2	1.2±0.3	1.3±0.6	0.19
<i>2 year</i>	1.25±0.40	1.2±0.2	1.2±0.2	1.4±0.8	0.70
<i>3 year</i>	1.30±0.43	1.2±0.2	1.3±0.2	1.5±0.8	0.58

Legend: IQR= interquartile range, SD= standard deviation, RBC= red blood cells, UOP= urine output. (¶) Median value was used for statistical calculation.

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**Figure 1: Patient Survival in Simultaneous (Group S) and Delayed (Group D)
Kidney Transplants in Combined Liver-Kidney Transplantation**

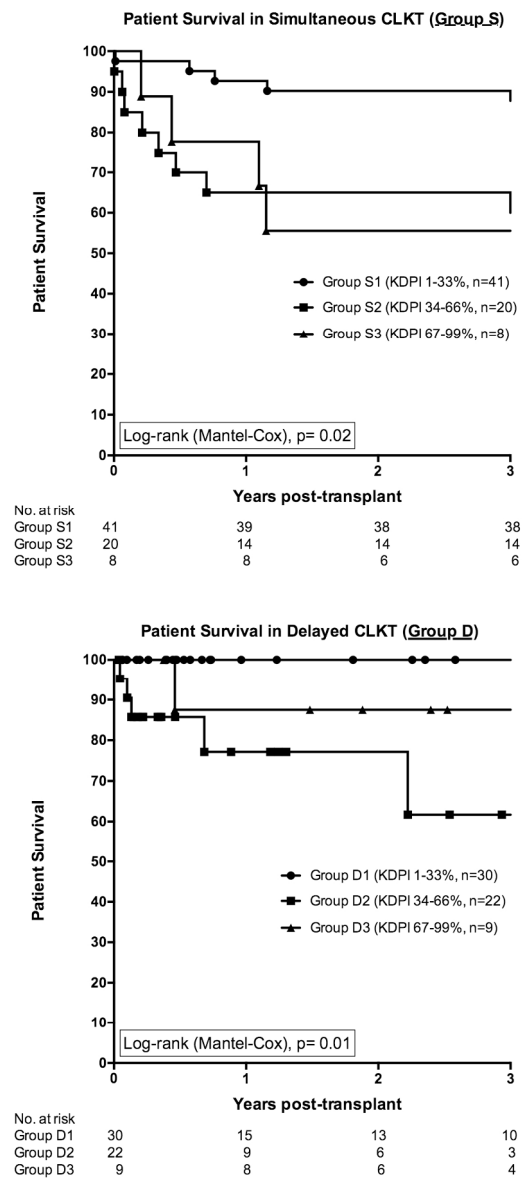


Figure 1: Patient Survival in Simultaneous (Group S) and Delayed (Group D) Kidney Transplants in Combined Liver-Kidney Transplantation

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